

REVIEW

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Silver nanoparticles are broad-spectrum bactericidal and virucidal compounds

Humberto H Lara^{1†}, Elsa N Garza-Treviño^{2†}, Liliana Ixtepan-Turrent² and Dinesh K Singh^{1*}**Abstract**

The advance in nanotechnology has enabled us to utilize particles in the size of the nanoscale. This has created new therapeutic horizons, and in the case of silver, the currently available data only reveals the surface of the potential benefits and the wide range of applications. Interactions between viral biomolecules and silver nanoparticles suggest that the use of nanosystems may contribute importantly for the enhancement of current prevention of infection and antiviral therapies. Recently, it has been suggested that silver nanoparticles (AgNPs) bind with external membrane of lipid enveloped virus to prevent the infection. Nevertheless, the interaction of AgNPs with viruses is a largely unexplored field. AgNPs has been studied particularly on HIV where it was demonstrated the mechanism of antiviral action of the nanoparticles as well as the inhibition the transmission of HIV-1 infection in human cervix organ culture. This review discusses recent advances in the understanding of the biocidal mechanisms of action of silver Nanoparticles.

Keywords: Silver Nanoparticles, Virucides, Bactericides, HIV/AIDS, Antibacterial agents

Review

Historically, silver metal has been used widely across the civilizations for different purposes. Many societies use silver as jewelry, ornamentation and fine cutlery. Silver, jewelry, wares and cutlery was considered to impart health benefits to the users. In ancient Indian medical system (Ayurveda) silver has been described as therapeutic agent for many diseases. There is an increasing use of silver as an efficacious antibacterial and antifungal agent in wound care products and medical devices [1-4] including dental work and catheters [5-7]. Another application is to synthesize composites for use as water disinfecting filters [8]. Silver is also appearing more frequently in textiles, cosmetics [9], and even domestic appliances. It is worth mentioning some examples, such as inorganic composites with a slow silver release rate, which are currently used as preservatives in a variety of cosmetic products [10]; another current application includes new compounds of silica gel microspheres containing a silver thiosulfate complex, which are mixed

into plastics for long-lasting antibacterial protection [11].

Metallic silver has also been used for surgical prosthesis and splints, fungicides, and coinage. Soluble silver compounds, such as silver salts, have been used for treating mental illness, epilepsy, nicotine addiction, gastroenteritis, stomatitis [12,13], and sexually transmitted diseases, including syphilis and gonorrhea [14]. Additionally, AgNO₃, as eye drops, have been utilized to prevent gonococcal ophthalmic *neonatorum* in newborns by pediatricians for centuries [15]. Other agents derived from silver, such as silver sulfadiazine (AgSD) cream, have been used by surgeons, as topical treatments to heal burn wounds, for the past 60 years [16,17]. Utilizing these topical treatments, applied directly to the burn site, erythema decreased, while the expression of matrix metalloproteinases (MMPs) increased [18]. Recent advances in nanotechnology have enabled us to produce pure silver, as nanoparticles, which are more efficient than silver ions (AgSD and AgNO₃) [19]. This has opened up whole new strategies to use pure silver against a wide array of pathogens, particularly multi-resistant pathogens which are hard to treat with available antibiotics. The biocidal activities of pure silver

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nanoparticles are discussed in subsequent sections of this review.

The multi-resistant pathogens due to antigenic shifts and/or drifts are ineffectively managed with current medications. This resistance to medication by pathogens has become a serious problem in public health; therefore, there is a strong need to develop new bactericides and virucides. Silver nanoparticles (AgNPs), having a long history of general use as an antiseptic and disinfectant, are able to interact with disulfide bonds of the glycoprotein/protein contents of microorganisms such as viruses, bacteria [20,21] and fungi [22]. Both silver nanoparticles and silver ions can change the three dimensional structure of proteins by interfering with S-S bonds and block the functional operations of the microorganism [23,24].

Silver Nanoparticles

Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-100 nm [25]. AgNPs can be dissolved in a liquid environment that prevents their agglomeration or entrapped in a matrix that utilizes special drug carrier systems (e.g., the drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix). These particles represent an interesting candidate for research as microbicides due to their effectiveness in small doses, minimal toxicity and side effects [26]. These attributes may contribute significantly to the enhancement of current prevention of infection and antiviral therapies [19,26].

Particle size and size distribution are the most important characteristics of nanoparticle systems (Figure 1). They determine the *in vivo* distribution, biological fate, toxicity and the targeting ability of nanoparticle systems [27]. Available routes of administration include oral, nasal, parenteral or intra-ocular [28]. Despite these advantages, nanoparticles do have limitations. For example, their small size and large surface area can lead to particle-particle aggregation, making physical handling of nanoparticles difficult in liquid and dry forms [29]. This aggregation may lead to the loss of the properties

associated with the nanoscale nature of the particles. The rate of agglomeration of nanoparticles is an important parameter for toxicology studies. Greulich *et al.* 2009 [30] reported that the agglomeration of AgNPs was specifically observed after the incubation of AgNPs in RPMI 1640 medium (a commonly used medium to dilute AgNPs) alone. However, washing AgNPs with RPMI 1640 medium containing Fetal Calf Serum (FCS) efficiently prevented agglomeration of AgNPs. Apart from agglomeration, particle sizes of AgNPs are also responsible for cytotoxicity. Yen *et al.* 2009 reported that smaller AgNPs (3 nm) are more cytotoxic than larger particles (25 nm) at a concentration of 10 µg/mL [31] signifying importance of particle size. Fukuoka and colleagues in an elegant experiment have demonstrated synthesis of necklace-shaped mono- and bimetallic nanowires for organic-inorganic hybrid mesoporous materials for better efficacy indicating not only the size of nanoparticle is important, but the shape and morphology are important as well [32]. Recent advances in Nanotechnology help in modulation of size and shape of nanoparticles and provide different ways of utilizing application of nanoparticles in diagnosis and treatment of various diseases. Using latest technology, Nanomaterials can also be tailored to facilitate their applications in other fields such as bioscience and medicine [3].

AgNPs as Antibacterial Agents

AgNPs are attractive because they are non-toxic to the human body at low concentrations and have broad-spectrum antibacterial actions [33]. In fact, it is well known that Ag⁺ ions and Ag-based compounds are toxic to microorganisms, possessing strong biocidal effects on at least 12 species of bacteria including multi-resistant bacteria like Methicillin-resistant *Staphylococcus aureus* (MRSA), as well as multidrug-resistant *Pseudomonas aeruginosa*, ampicillin-resistant *E. coli* O157: H7 and erythromycin-resistant *S. pyogenes* [2,4,21] suggesting that AgNPs are effective broadspectrum [34] biocides against a variety of drug-resistant bacteria, which makes them a potential candidate for use in pharmaceutical products and medical devices that may help to prevent the transmission of drug-resistant pathogens in different clinical environments [2,35]. Recently, Mecking and co-workers demonstrated that hybrids of silver nanoparticles with amphiphilic hyperbranched macromolecules exhibited effective antimicrobial surface coating agent properties [36].

The mechanism of the inhibitory effects of Ag⁺ ions on microorganisms is not completely clear, however, AgNPs interact with a wide range of molecular processes within microorganisms resulting in a range of effects from inhibition of growth, loss of infectivity to cell death which depends on shape [37], size [31],

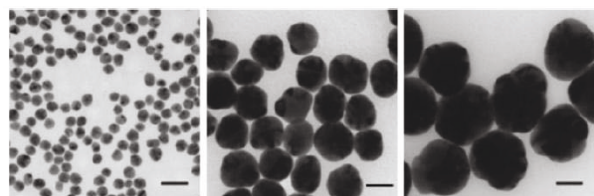


Figure 1 Transmission electron microscopy (TEM) images of silver nanoparticles with diameters of 20 nm (Aldrich), 60 nm (Aldrich), and 100 nm (Aldrich), respectively. Scale bars are 50 nm.

concentration of AgNPs [38] and the sensitivity of the microbial species to silver [2,17,35,39-41]. Several studies have reported that the positive charge on the Ag⁺ ion is crucial for its antimicrobial activity through the electrostatic attraction between the negatively charged cell membrane of the microorganism and the positively charged nanoparticles [1]. In contrast, Sondi and Salopek-Sondi reported that the antimicrobial activity of AgNPs on Gram-negative bacteria depends on the concentration of AgNPs and is closely associated with the formation of pits in the cell wall of bacteria [21]; consequently, AgNPs accumulated in the bacterial membrane disturbing the membrane permeability, resulting in cell death. However, because those studies included both positively charged Ag⁺ ions and negatively charged AgNPs, this data is insufficient to explain the antimicrobial mechanism of positively charged silver nanoparticles. Therefore, we theorize that there is another possible mechanism. Amro *et al.* suggested that metal depletion may cause the formation of irregularly shaped pits in the outer membrane and change membrane permeability, which is caused by the progressive release of lipopolysaccharide molecules and membrane proteins [42]. Also, Sondi and Salopek-Sondi speculated that a similar mechanism may cause the degradation of the membrane structure of *E. coli* during treatment with AgNPs [21]. Although it is assumed that AgNPs are involved in some sort of binding mechanism, the mechanism of the interaction between AgNPs and components of the outer membrane is still unclear. Recently, Danilczuk and co-workers reported that Ag-generated free radicals derived from the surface of AgNPs were responsible for the antimicrobial activity [43]. However, Lara and colleagues in another report, proposed another mechanism of bactericidal action based on the inhibition of cell wall synthesis, protein synthesis mediated by the 30s ribosomal subunit, and nucleic acid synthesis [2]. The proteomic data revealed that a short exposure of *E. coli* cells to antibacterial concentrations of AgNPs resulted in an accumulation of envelope protein precursors, indicative of the dissipation of proton motive force [44]. Consistent with these proteomic findings, AgNPs were shown to destabilize the outer membrane, collapse the plasma membrane potential and deplete the levels of intracellular ATP [45].

The mode of action of AgNPs was also found to be similar to that of Ag⁺ ions [45]; however, the effective concentrations of silver nanoparticles and Ag⁺ ions were at nanomolar and micromolar levels. Therefore results in *E. coli* suggested silver nanoparticles may damage the structure of bacterial cell membrane and depress the activity of some membranous enzymes, which cause *E. coli* bacteria to die eventually [46].

Silver Nanoparticles as Virucidal Agents

Virucidal agents differ from virustatic drugs in that they act directly and rapidly by lysing viral membranes on contact or by binding to virus coat proteins. Nevertheless, the interaction of AgNPs with viruses is still an unexplored field. However, the mechanism of action of AgNPs as an antiviral and virucidal has been studied against several enveloped viruses. Recently, it has been suggested that nanoparticles bind with a viral envelope glycoprotein and inhibit the virus by binding to the disulfide bond regions of the CD4 binding domain within the HIV-1 viral envelope glycoprotein gp120, as suggested by Elechiguerra and colleagues [47]. This fusion inhibition was later elegantly demonstrated by Lara and colleagues [19] in their latest report.

The antiviral effects of AgNPs on the hepatitis B virus (HBV) have been reported using a HepAD38 human hepatoma cell line. There has been evidence of high binding affinity of nanoparticles for HBV DNA and extracellular virions with different sizes (10 and 50 nm). Moreover, it has been demonstrated that AgNPs could also inhibit the production of HBV RNA and extracellular virions *in vitro*, which was determined using a UV-vs absorption titration assay. Further investigation will be needed to determine whether this binding activity prevents HBV virions from entering into host cells or not [39]. In another report Sun and colleagues showed that AgNPs were superior to gold nanoparticles for cytoprotective activities toward HIV-1-infected Hut/CCR5 cells [48]. It is generally understood that Ag, in various forms, inactivates viruses by denaturing enzymes via reactions with sulfhydra, amino, carboxyl, phosphate, and imidazole groups [33,34,36,41,49]. However, it is necessary to design studies *in vivo* to increase therapeutic benefit and minimize adverse effects.

Among antiviral activities, the capacity of AgNPs to inhibit an influenza virus was determined in a MDCK cell culture and was demonstrated that with AgNPs at 0.5 µg/ml concentration viral infectivity was reduced. Nanosilver may interfere with the fusion of the viral membrane, inhibiting viral penetration into the host cell [40].

Lara and colleagues further demonstrated that AgNPs inhibited a variety of HIV-1 strains regardless of their tropism, clade and resistance to antiretrovirals [19]. The fact that AgNPs inhibited number of HIV-1 isolates suggest that their mode of action does not depend on cell tropism and that AgNPs are broad spectrum anti-HIV-1 agents. A cell-based fusion assay using Env expressing cells (HL2/3) and CD4 expressing cells mixture demonstrated that AgNPs efficiently blocked cell-cell fusion in a dose-dependent manner within the 1.0-2.5 mg/mL dose range including: Tak-779 (Fusion Inhibitor), AZT (NRTI), Indinavir (PI) and 118-D-24 (Integrase

Inhibitor) as controls (Figure 2). In addition, efficient inhibitory activity of AgNPs against gp120-CD4 interaction was measured in a competitive gp120-capture ELISA. The results of the cell-based fusion assay confirm the hypothesis that AgNPs inhibit HIV-1 infection by blocking the viral entry, particularly the gp120-CD4

interaction [19]. Other studies also showed that AgNPs at non-toxic concentrations effectively inhibit arenavirus replication during the early phases of viral replication [50].

Continuing to assess antiviral mechanisms, a virus adsorption assay was performed to measure the

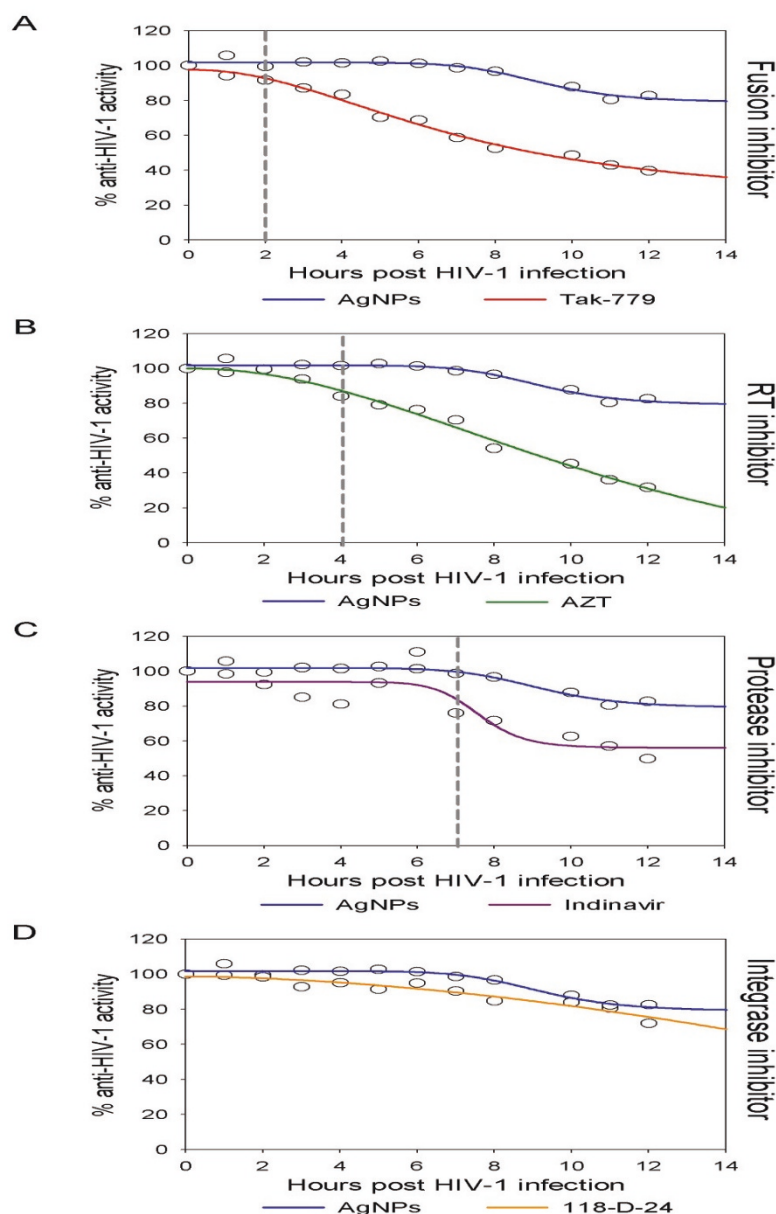


Figure 2 Time-of-addition experiment. HeLa-CD4-LTR- β -gal cells were infected with HIV-1_{IIIB} and exposed to silver nanoparticles (1 mg/mL). Different antiretrovirals were added at different times post infection. Activity of silver nanoparticles was compared with (A) fusion inhibitor (Tak-779, 2 μ M), (B) RT inhibitor (AZT, 20 μ M), (C) protease inhibitor (Indinavir, 0.25 μ M), and (D) integrase inhibitor (118-D-24, 100 μ M). Dashed lines indicate the moment when the activity of the silver nanoparticles and the antiretroviral differ. The assays were performed in triplicate; the data points represent the mean and the colored lines are nonlinear regression curves performed with SigmaPlot 10.0 software. <http://www.jnanobiotechnology.com/content/8/1/1/figure/F2>

inhibitory effects of AgNPs on virus adsorption to HeLa-CD4-LTR- β -gal cells, which were incubated with HIV_{IIIB} in the absence or presence of serial dilutions of AgNPs. After 2 h of incubation at 37°C, the cells were extensively washed with 1× PBS to remove the unadsorbed virus particles. Then the cells were incubated for 48 h, and the amount of viral infection was quantified with the Beta-Glo Assay System (Promega). The AgNPs inhibited the initial stages of the HIV-1 infection cycle of HIV_{IIIB} virus to cells with an IC₅₀ of 0.44 mg/mL.

Cell-free and cell-associated HIV-1 were pretreated at different concentrations of AgNPs, and were centrifuged and washed to separate the virus from the AgNPs and then infect the indicator cells. The cell-associated virus includes infected cells that transmit the infection by fusing with non-infected target cells. In addition, AgNPs treatment of chronically infected H9+ cells as well as human PBMC+ (cell-associated HIV) resulted in decreased infectivity in a dose-dependent manner [19].

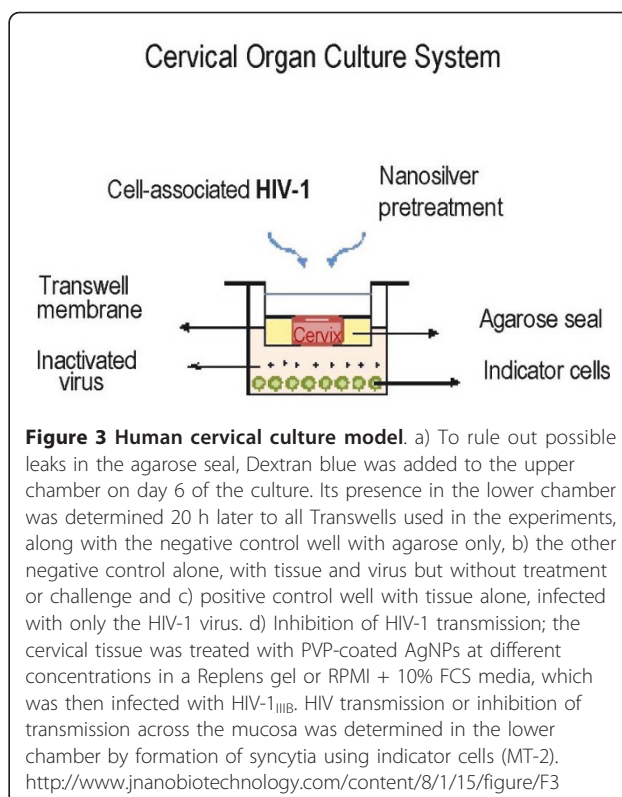
Time-of-addition experiments (TAE) for HIV revealed that silver nanoparticles have other sites of intervention on the viral life cycle besides fusion or entry (Figure 2). This could be explained by silver nanoparticles suppressing the expression of TNF- α , a cytokine that plays a critical role in HIV-1 pathogenesis, by incrementing HIV-1 transcription. The inhibition of the TNF- α activated transcription might also be a target for the anti-HIV activity of silver nanoparticles. Having a variety of targets in the HIV-1 replication cycle makes silver nanoparticles agents that are not prone to contribute to the emergence of resistant strains [26].

The Antiviral Effect of AgNPs as a Topical Agent on Human Cervical Tissue

In an experiment evaluating AgNPs application on Human cervical tissue as an anti-HIV-1 agent, Lara and colleagues [26] found that AgNPs provided protection against the transmission of cell-free and cell-associated HIV-1. They had used an excellent human cervical tissue culture model to elucidate anti-HIV-1 activity of AgNPs within one minute after the topical treatment on the human cervical tissue (Figure 3). The similar effect was found for 20 minutes time point of topical pretreatment and washing of the AgNPs. The human cervical tissue culture remained protected against infection with HIV-1 for as long as 48 h, demonstrating a long-lasting tissue protection afforded by AgNPs. This lasting protection is necessary for a topical vaginal microbicide to ensure safety against infection even for many hours after gel application and, even more importantly, after the gel is washed away (Figure 4) [26].

AgNPs as Topical Agents in Mucosal Human Tissue

Recent studies showed that pre-treatment of human cervical tissues with AgNPs increased the proliferation of



lymphocytes, presumably due to activation of the immune cells [26,14,51,52]. The increased proliferation of lymphocytes also increases inflammatory process *in situ* by contributing in wound healing *in vivo* [53]. The development of inflammatory process in cervical tissue helps activation of innate defenses against invading microbes. These changes during inflammation in cervical tissue are chiefly regulated under hormonal conditions by estradiol and progesterone [54,55]. Further studies are necessary to evaluate topical use of nanoparticles applied repeatedly to record chronic response, toxicity (i.e., genetic, reproductive, and carcinogenic toxicities) and long-term side effects, susceptibility to opportunistic infections or significant changes in tissue architecture. Studies should also be performed to evaluate occurrence of any hypersensitivity/photosensitivity and AgNPs effect on condom integrity before AgNPs can be included in a topical gel for human use [56,57].

AgNPs cytotoxicity

The AgNPs have been shown to be cytotoxic at higher concentration than 6 μ g/mL. Hsin and colleagues provided evidence for the molecular mechanism of AgNPs induction of cytotoxicity. They showed that AgNPs acted through ROS and JNK to induce apoptosis via the mitochondrial pathway in NIH3T3 fibroblast cells [58]. Park and colleagues reported cytotoxicity using

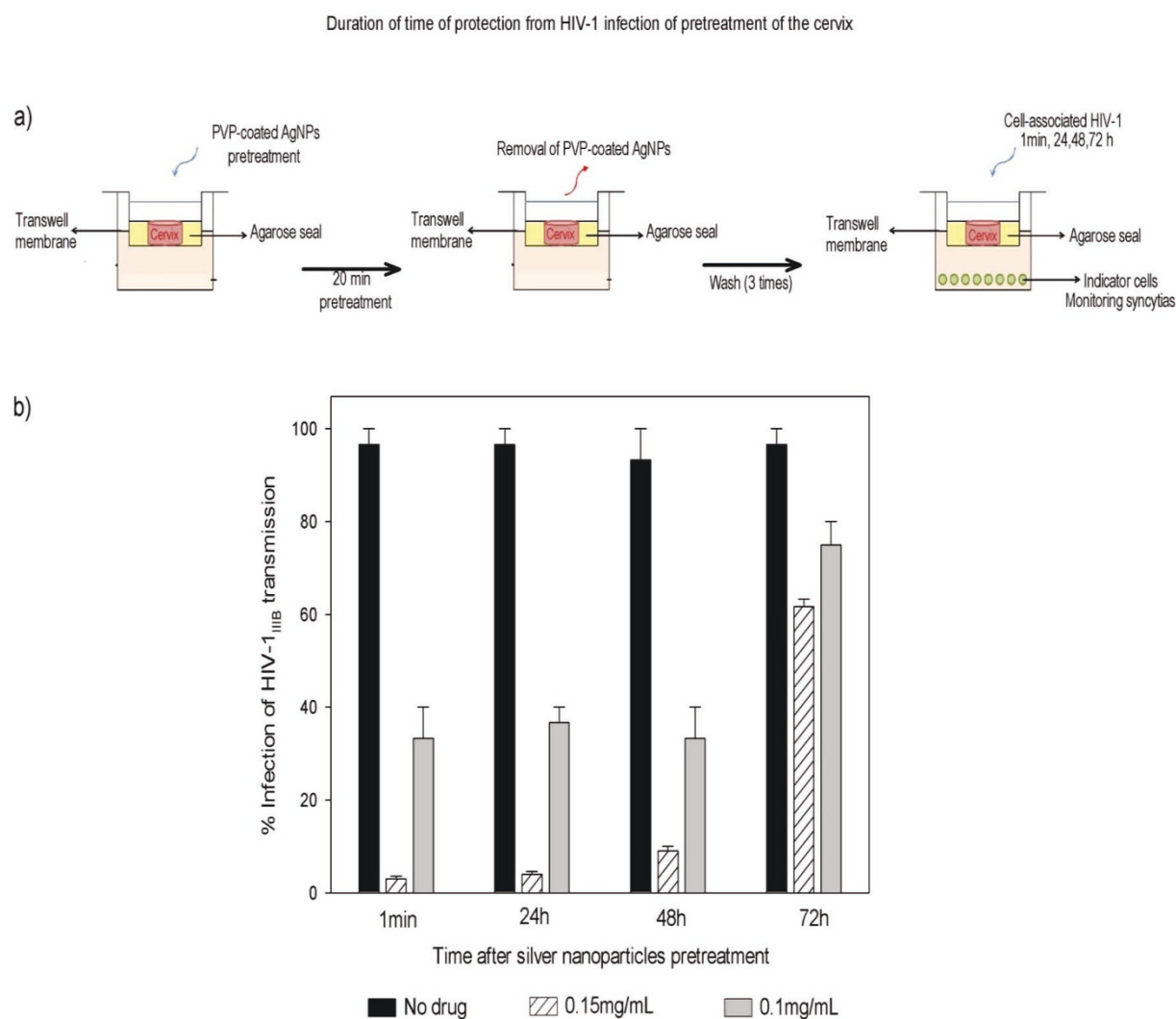


Figure 4 Protection from HIV-1 infection following pre-treatment of the cervical explant with PVP-coated AgNPs. a) Cervical explants were exposed to 0.1 or 0.15 mg/mL PVP-coated AgNPs in RPMI + 10% FCS media for 20 minutes. After thoroughly washing extracellular PVP-coated AgNPs from the cervical explant, and after 1 minute, 24 h, 48 h and 72 h, cell-free virus (HIV-1_{IIIIB}) [$(5 \times 10^5$ TCID₅₀)] was added to the upper chamber. To verify the neutralization of HIV-1 transmission, we cultured the indicator cells (MT-2) in the lower chamber and evaluated the inhibition of the HIV-1 infection. b) Cervical explants were exposed to HIV-1 in the absence of PVP-coated AgNPs as a control and to 0.1 or 0.15 mg/mL of PVP-coated AgNPs as pretreatment. Graphs show values of the means \pm standard deviations from three separate experiments. Graphs were created using the SigmaPlot 10.0 software. <http://www.jnanobiotechnology.com/content/8/1/15/figure/F5>

silver nanoparticles prepared by dispersing them in fetal bovine serum, as a biocompatible material, on a cultured macrophage cell line, which induced cellular apoptosis [59]. Furthermore, AgNPs decreased intracellular glutathione levels, increased NO secretion, increased TNF- α protein and gene levels, and increased the gene expression of matrix metalloproteinases, such as MMP-3, MMP-11, and MMP-19. Kim and colleagues demonstrated cytotoxicity induced by AgNPs in human hepatoma HepG2 cells and observed that AgNPs agglomerated in the cytoplasm and nuclei

of treated cells, and induced intracellular oxidative stress, independent of the toxicity of the Ag⁺ ions [1]. In a similar study, Kawata and colleagues showed an upregulation of DNA repair-associated genes in hepatoma cells cultured with low dose AgNPs, suggesting possible DNA damaging effects [60,61]. Recent studies demonstrated that uptake of AgNPs occurs mainly through clathrin mediated endocytosis and macropinocytosis [38], however it seems that AgNPs have multiple cellular targets that vary among different cell types.

Conclusions

The emergence and spread of antibiotic resistance pathogen is an alarming concern in clinical practice. Many organisms such as MRSA, HIV-1, Hepatitis-B Virus, and Ampicillin resistant *E.coli* are difficult to treat. There is a need of a cheap broad-active agent that can be used against variety of pathogen. The AgNPs have been found to be effective against many viruses and bacterial species. The use of noble metals at nano-sizes to treat many conditions is gaining importance. The recent development in nanotechnology has provided tremendous impetus in this direction due to its capacity of modulating metals into nanosizes and various shapes, which drastically changes the chemical, physical and optical properties and their use. The efficacy of AgNPs against HIV-1 has been reported by many laboratories including ours [19,26]. It has been shown that AgNPs have got anti-HIV-1 activity and can help the host immune system against HIV-1. This has laid ground for the development of new, potent antiviral drugs capable of preventing HIV infection and controlling virus replication. Recently, it has been demonstrated that AgNPs function as broad-spectrum virucidal and bactericidal agents, and in addition, increase wound healing. Nonetheless, conclusive safety has not been demonstrated extensively in animal models, and therefore, additional testing of AgNPs is needed before they can be used in clinical applications.

Authors Information

DKS: is an associate professor of microbiology at the Winston Salem State University. DKS' lab is working on development of a DNA vaccine for HIV/AIDS. His other research interest involves prevention of HIV-1 transmission at the cervical/vaginal mucosal surfaces. His current research is funded by two NIH grants.

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Authors' contributions

All authors read and approved the final manuscript. HHL participated in AgNPs cytotoxicity, AgNPs as topical agents in mucosal human tissue, and overall design of this review article. ENG participated in AgNPs as antibacterial agent portion of this review, and overall design of this review article along with HHL. LIT participated in antiviral effect of AgNPs as a topical agent on Human cervical tissue. DKS participated in AgNPs as virucidal agents, and editing and revision of this report. His lab provided materials and resources used in this study.

Competing interests

The authors declare that they have no competing interests.

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